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● *Review Article*

VASCULAR SHEAR WAVE ELASTOGRAPHY IN ATHEROSCLEROTIC ARTERIES: A SYSTEMATIC REVIEW

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Abstract—Ischemic stroke is a leading cause of death and disability worldwide, so adequate prevention strategies are crucial. However, current stroke risk stratification is based on epidemiologic studies and is still suboptimal for individual patients. The aim of this systematic review was to provide a literature overview on the feasibility and diagnostic value of vascular shear wave elastography (SWE) using ultrasound (US) in (mimicked) human and non-human arteries affected by different stages of atherosclerotic diseases or diseases related to atherosclerosis. An online search was conducted on Pubmed, Embase, Web of Science and IEEE databases to identify studies using US SWE for the assessment of vascular elasticity. A quality assessment was performed using Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) checklist, and relevant data were extracted. A total of 19 studies were included: 10 with human patients and 9 with non-human subjects (*i.e.,* [excised] animal arteries and polyvinyl alcohol phantoms). All studies revealed the feasibility of using US SWE to assess individually stiffness of the arterial wall and plaques. Quantitative elasticity values were highly variable between studies. However, within studies, SWE could detect statistically significant elasticity differences in patient/subject characteristics and could distinguish different plaque types with good reproducibility. US SWE, with its unique ability to assess the elasticity of the vessel wall and plaque throughout the cardiac cycle, might be a good candidate to improve stroke risk stratification. However, more clinical studies have to be performed to assess this technique's exact clinical value. (E-mail: Judith.Pruijssen@radboudumc.nl)

Key Words: **Systematic literature review, Shear wave elastography, Atherosclerosis, Ultrasound.**

INTRODUCTION

Worldwide, 13.7 million people experience a stroke each year; it is the second leading cause of death and disability (Global Burden of Disease Study [GBDS] Collaborators 2019). Approximately 80% of all strokes are ischemic (GBDS Collaborators 2019), and 10%–20% of ischemic strokes are caused by carotid artery atherosclerosis (Flaherty et al. 2013). To reduce the (recurrent) ischemic stroke risk, a carotid endarterectomy (CEA) is performed, based mainly on age, comorbidity, presence of neurologic symptoms, and detection of a stenosis of the ipsilateral carotid artery >70% by duplex ultrasound or computed tomography angiography (CTA) (Chaturvedi et al. 2005). However, this selection based on degree of stenosis is not perfect because, for stenoses >70%, on average only one stroke is prevented for each six patients undergoing a CEA (Chaturvedi et al. 2005). This is considerable because it is a rather risky procedure given its peri-operative risk of stroke or death of 3%–8% (Chaturvedi et al. 2005).

To improve risk stratification, research interest has shifted from degree of stenosis to plaque stability and vulnerability because of increased evidence that non-stenotic, unstable atherosclerotic plaques are more vulnerable to embolization, regardless of degree of stenosis (Freilinger et al. 2012). Additionally, many patients with a high degree of stenosis seem to have a low risk of plaque rupture (Horie et al. 2012). On the basis of pathologic features, plaques are classified as vulnerable or stable, and are likely and unlikely to rupture, respectively. Vulnerable plaques are defined by a large lipid-

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rich core separated from the lumen by a thin fibrous cap infiltrated with active inflammation, so called thin-cap fibroatheromas. Stable plaques are typically composed of a fibrous core and thick fibrous cap (Spagnoli et al. 2004; Fisher et al. 2005).

To implement pathologic features in the risk stratification before surgery, image-based studies have focused on their non-invasive assessment. Currently, magnetic resonance imaging (MRI) is the gold standard in the assessment of carotid plaque vulnerability because of its high sensitivity in detecting histologic features associated with vulnerability, but it is hindered by time constraints, contraindications and costs (Brinjikji et al. 2015), and has a limited resolution of 0.7 mm (isotropic) *in vivo* using dedicated coils (Coolen et al. 2016). This resolution limits the determination of individual plaque components, especially in case of a mild (<50%) carotid artery stenosis, the rupture of which is also considered to cause a substantial proportion of strokes (Coutinho et al. 2016). In contrast, ultrasound is a cost-effective technique to assess stenosis degree, plaque morphology and plaque characteristics that is already widely incorporated in stroke risk assessment (Brinjikji et al. 2015), and has at least a two times better resolution than MRI. Additional parameters have also been studied using ultrasound, and symptomatic ischemic strokes were associated with an increased carotid intima−media thickness (IMT), plaque neovascularity, ulceration, echolucency (gray-scale median [GSM]), and intraplaque motion (Brinjikji et al. 2015). Although these parameters are based on the pathologic features described above, ultrasound techniques capable of directly assessing mechanical plaque properties are still missing in daily clinical practice.

Ultrasound elastography is an emerging technique that directly quantifies plaque mechanics, that is, tissue stiffness, and is therefore a potential candidate tool in the assessment of plaque vulnerability. Elastography includes both strain imaging and shear wave elastography (SWE) (Bamber et al. 2013; Hansen et al. 2016). In SWE an acoustic radiation force push pulse, the so-called acoustic radiation force impulse (ARFI) push pulse, is used to induce a shear wave (Sarvazyan et al. 1998). This shear wave propagates perpendicular to the push pulse and can be imaged while it propagates through the tissue using ultrafast plane wave acquisitions. The velocity by which it propagates is directly related to the tissues' elasticity expressed by the Young's modulus (YM) (Bamber et al. 2013). The stiffer the tissue, the higher is the YM, and the higher is the shear wave velocity (SWV). Because YM is significantly lower for fatty tissue than for fibrotic tissue (Chai et al. 2013), SWE is a potential candidate tool to improve vulnerable plaque detection and, therefore, to improve stroke risk stratification.

For large linearly elastic tissues, every frequency component of the shear wave propagates at the same speed. Because of this independence of frequency, the velocity of the shear wave front can be tracked as a whole, providing the group SWV (Graff 1991). This so-called group velocity analysis is performed in all current commercial SWE devices, Therefore, we are referring to the group SWV when we refer to SWV in this article. In heterogeneous, thin and anisotropic material such as arteries, the assumptions made by the clinical scanners are not entirely valid. The frequency components of the induced waves propagate with (slightly) different velocities, a phenomenon called dispersion. To account for dispersion, so-called phase velocity analysis can be performed; that is, velocity is assessed per frequency (Graff 1991). Models describing dispersion can then be fitted to these phase velocities to obtain an estimate of the YM (Couade et al. 2010; Bernal et al. 2011).

The aim of this systematic review was to provide an overview of the available literature on the feasibility and diagnostic value of using vascular SWE in (mimicked) human and non-human arteries affected by different stages of atherosclerotic diseases or diseases related to atherosclerosis.

METHODS

Search strategy and study selection

To retrieve all available studies on the vascular application of SWE in atherosclerotic diseases, an online literature search was performed in Pubmed, Web of Science, Cochrane library, Embase and IEEE databases on March 25, 2020. This search was based on three key words: Shear wave elastography, Ultrasound, and Atherosclerosis. As an example, the entry terms for the PubMed search, combined by "AND," are listed in Table 1. The same synonyms were used in the remaining databases. Two authors independently

Table 1. Entry term searches

Key word	MeSH term	Free text entry term
Ultrasound	"ultrasonography"	echograph*[tiab] OR ultrasound[tiab] OR sonograph*[tiab] OR verasonic*[tiab] OR supersonic*[tiab]
Atherosclerosis	"atherosclerosis" OR "plaque, atherosclerotic"	plaque*[tiab] OR fatty streak*[tiab] OR atheroscleros*[tiab] OR arterioscleros*[tiab]
Shear wave elastography	"elasticity imaging techniques"	shear wave*[tiab] OR shear wave elastograph*[tiab] OR shear modul*[tiab] OR elastic modul*[tiab] OR shear imaging[tiab]

reviewed all titles and abstracts for eligibility. Subsequently, the same authors retrieved full texts of potentially relevant articles for further evaluation. Additionally, they conducted a manual selection of potentially eligible studies from the reference lists of included studies. Inclusion was based on the following criteria: (i) English language, (ii) *in vivo, ex vivo* or *in vitro* phantom studies involving or mimicking arteries with atherosclerotic disease or diseases related to atherosclerosis using ultrasound SWE, and (iii) assessment of YM or SWV. Exclusion was based on the following criteria: (i) editorials, (ii) reviews, (iii) letters to the editor, (iv) case reports on fewer than five patients, (v) articles on mathematical optimization of SWE, (vi) articles not using SWE to assess elasticity, and (vii) in case of *in vivo* studies, no informed consent from each study participant and protocol approval by an ethics committee or institutional review board (human studies) or institutional animal care and use committee (animal studies) mentioned. When the two reviewers did not agree, a third reviewer was consulted to decide on inclusion or exclusion.

Data extraction and quality assessment

After inclusion, one author systematically extracted relevant data regarding each publication, pre-defined as (i) year of publication, (ii) country of research, (iii) number of included patients, (iv) subject characteristics (*i.e.,* for humans, age and sex; for animals, imaged artery; for phantoms, percentage of polyvinyl alcohol [PVA] and number of freeze−thaw cycles), (v) imaging characteristics (*i.e.,* type of ultrasound system and probe, imaging and push frequency, push duration, push location and scan direction), (vi) reference standard, (vii) use of electrocardiogram (ECG) gating, (viii) values of SWV/YM/shear modulus and (ix) most important results (*e.g.,* correlations of YM and plaque characteristics or accuracy). Quality assessment of human studies was performed by one author using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) checklist (Whiting et al. 2011), a standardized and validated tool used to assess quality and risk of bias of diagnostic accuracy studies. Because non-human studies do not match criteria of a standardized checklist, qualitative assessment of these studies was not performed. Conference abstracts and proceedings were individually analyzed, and additional items that are not discussed in the included full articles are stated in the Results because they are not peer-reviewed and do not contain all methodological information.

RESULTS

Study characteristics

A flowchart of data selection is provided in Appendix A (online only, see Supplementary Data). With the initial database search and reference evaluation, 838 individual studies were identified. 45 published articles were selected based on title and abstract and further screened on full-text reading. 26 articles were excluded for reasons stated in Appendix A (online only, see Supplementary Data). Eventually, 19 published articles were included for qualitative assessment and data extraction. These studies were divided according to the subjects involved: human subjects or non-human subjects (*i.e.,* [excised] animal arteries or phantoms). Extracted data for human and non-human studies are listed in Tables 2 and 3, respectively. Eighteen conference abstracts and seven proceedings were selected based on title and abstract. After screening for publication of these studies, respectively 11 and 2 conference abstracts and proceedings were included and further analyzed. Extracted data for these studies are listed in Appendix B (online only, see Supplementary Data). A meta-analysis was not conducted because of the heterogeneity of study type, types of patients included, methods and reported results.

Quality assessment

An overview of the qualitative assessment of included human studies is provided in Appendix C (online only, see Supplementary Data). All studies scored an unknown or high risk of bias in at least one category. Seven studies (Ramnarine et al. 2014b; Garrard et al. 2015; Li et al. 2016; Zhang et al. 2016; Alis et al. 2018; Shang et al. 2018; Marlevi et al. 2020) did not report whether they included patients randomly or consecutively, and one study reported they did not (Marais et al. 2019). In addition, most studies (Li et al. 2016; Zhang et al. 2016; Lou et al. 2017; Marais et al. 2019) did not report whether the index test was interpreted without knowledge of the reference standard and vice versa. Additionally, multiple studies (Ramnarine et al. 2014b; Zhang et al. 2016; Lou et al. 2017; Shang et al. 2018) used echogenicity as a reference standard in assessment of plaque vulnerability. However, echogenicity provides only an indication of plaque composition; it does not absolutely assess it. Di Leo et al. (2018) did not mention any quantitative values measured by the index test, which complicates the assessment of whether its interpretation could have introduced bias. Finally, two studies (Ramnarine et al. 2014b; Shang et al. 2018) did not include all patients in the final analysis because of complete occlusion of the internal carotid artery (ICA) and presence of both hyper- and hypo-echoic plaques on the symptomatic side. Marais et al. (2019) also did not include all patients in the final analysis but they argued that the included subpopulation was representative of the entire population. This minimizes the chance of bias induced by patient flow. Overall, the main sources of bias related to this review could be the selection of patients and the use of echogenicity, which is not a gold

Table 2. Characteristics of human studies included

Reference	Country	No. of patients	Age (y)*	♂ (%)	Scanner; probe; frequency; push duration; push location; direction	ECG trigger	Comparison†	Mean SWV/YM*,‡	Most important findings
Marlevi et al. 2020	Sweden	20 + stress echocardiography + plaques; 27 plaques	68 ± 8	16 (80)	General Electric Logiq E9, L9 MHz probe; 4.1- or 5.0-MHz push; 400 μs; left- and right-side ROI; longitudinal + transversal	No	**MRI (AHA classification)**	Plaque: Group velocity (L/T): *V* (n = 8): 4.0 ± 1.1/3.3 ± 0.7 m/s (YM: 50 ± 4/34 ± 2 kPa) *VI* (n = 8): 5.8 ± 0.6/7.3 ± 2.5 m/s (YM: 105 ± 1/166 ± 20 kPa) Phase velocity (400−500 Hz) (L/T): *V*: 4.1 ± 1.9/4.3 ± 1.4 m/s (YM: 52 ± 11/58 ± 6); *VI*: 7.0 ± 1.4/5.2 ± 2.1 m/s (YM: 153 ± 6/84 ± 14 kPa)	Vulnerable plaques (AHA-VI) higher group and phase velocity (400−500 Hz) than other plaque types Group and phase velocity (400−500 Hz) correlated with Intraplaque components: LRNC content, fibrous cap structure, IPH Phase velocity (300−400 Hz) → negative correlation with IPH volume Findings differed between longitudinal and transverse plane imaging
Marais et al. 2019	France	29 essential HT; 27 NT controls	49 ± 12 50 ± 12	14 (48) 15 (56)	Aixplorer (Supersonic), L8 MHz probe, FR 8 kHz; 3 × 100 μs; 3 depths 5 mm apart in center ROI including anterior and posterior wall; longitudinal	Yes	Normotensive controls **Arterial tonometry (PWV)**	*Wall (anterior/posterior):* *HT*: 5.9 ± 0.9/6.8 ± 1.4 m/s *(YM: 108.6 ± 2.5/144.3 ± 6.1 kPa‡)* *NT:* 5.2 ± 1.0/7.4 ± 2.4 m/s *(YM: 84.4 ± 3.1/170.9 ± 18.0 kPa‡)*	aSWV (positively) associated with age and BP, pSWV not aSWV increased with BP throughout cardiac cycle, no difference in NT and HT with similar BP SWV had good agreement with PWV (Spearman correlation $r = 0.56-0.66$) pSWV higher inter-acquisition variability than SWV (20.5% vs. 8.3%, resp.)
Di Leo et al. 2018	Italy	43 scheduled CEAs	NR	NR	Toshiba Aplio 500, L14-5 MHz probe; NR; NR; longitudinal	No	**Histology** CTA	NR§ (vulnerable¶ n = 31, stable n = 12)	SWE high sensitivity (87.1%), but lower specificity than CTA (66.7% vs. 100%) AUC (SWE) = 76.9%, AUC (CTA) = 93.5% SWE had high agreement with CTA (81.4%, Cohen's $\kappa = 0.58$)

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Table 2 (***Continued***)

Reference	Country	No. of patients	Age (y)*	♂ (%)	Scanner; probe; frequency; push duration; push location; direction	ECG trigger	Comparison†	Mean SWV/YM*,‡	Most important findings
Shang et al. 2018	China	142 strokes + plaques	66 [57−62]	76 (54)	Aixplorer (Supersonic), L15-4 MHz probe; NR; NR; longitudinal	No	**Echogenicity** Homocysteine level Neurologic symptoms	Plaque: *Hypo-echoic (n = 78)*: 2.09 [1.69−2.41] *m/s (YM: 113.6 [8.9−18.1] kPa†)* *Hyper-echoic (n = 51)*: 4.29 [3.98−4.57] m/s *(YM: 57.4 [49.4−65.2] kPa†)*	SWV lower in hypo- than hyper-echoic plaques (Lower) mean SWV was related to symptomatic‖ ischemic stroke SWV differences in echogenicity not related to plaque depth Serum homocysteine levels negatively correlated with minimal SWV
Alis et al. 2018	Turkey	34 Behcets disease; 28 controls	40 ± 10 36 ± 8	18 (53) 15 (54)	Toshiba Aplio 500, L14-7 MHz probe; NR; NR; longitudinal	No#	Healthy controls	Wall (right/left): *Behcets disease:* 3.72 ± 0.94/3.57 ± 0.72 m/s *(YM: 34.2 ± 2.8/39.8 ± 0.8 kPa†* *Controls*: 2.42 ± 0.49/2.56 ± 0.49 m/s *(YM: 18.3 ± 0.75/ 20.4 ± 0.7 kPa†)*	Mean SWV higher in right and left CCA in patients than controls SWV did not correlate with cIMT
Lou et al. 2017	China	61+ plaques; 271 plaques**	66 ± 8	45 (74)	Aixplorer (Supersonic), L10−2 MHz probe; NR; NR; longitudinal	No	**Echogenicity (GSM)** Neurologic symptoms	Plaque: *GSM:* 1 (n = 13): 70.74; 2 (n = 35): 78.83; 3 (n = 195): 129.80; 4 (n = 21): 118.75; 5 (n = 7): 169.43 kPa *Symptomatic (n = 31)‖:* 81.13 ± 20.12 kPa *Asymptomatic (n = 30)*: 115.78 ± 26.66 kPa	SWV correlated with GSM (lower SWV in lower GSM) Mean YM lower in symptomatic than asymptomatic patients YM + SR best to predict symptomatic plaques AUC (YM) = 0.87, AUC (YM + SR) = 0.93, AUC (GSM) = 0.76 Perfect reproducibility YM with SWE (inter-frame CV = 16%)

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Table 2 (***Continued***)

Reference	Country	No. of patients	Age (y)*	♂ (%)	Scanner; probe; frequency; push duration; push location; direction	ECG trigger	Comparison†	Mean SWV/YM*,‡	Most important findings
Zhang et al. 2016	China	199 + plaques; 277 plaques	66 ± 11	105 (53)	Aixplorer (Supersonic), L10-2 MHz probe; NR; NR; longitudinal	No	**Echogenicity** Cardiovascular risk factors (HT, hyperlipidemia)	Plaque (proximal/distal shoulder/peak middle): *Hypo-echoic (n = 137)*: 15.7 ± 8.2/17.4 ± 8.7/11.3 ± 7.5 kPa *Hyper-echoic (n = 140):* 51.8 ± 16.3/50.8 ± 19.3/ 56.6 ± 17.0 kPa	YM lower in hypo- than hyper-echoic plaques YM values differ with plaque site YM lower in all plaques in case of HT + hyperlipidemia/hyperlipidemia alone, YM also lower in hypo-echoic plaques in case of HT Excellent reproducibility YM with SWE (ICC = 0.92−0.95)
Maksuti et al. 2016	China	175 <7 days after AIS; 168 controls	65 ± 10 65 ± 8	99 (57)	Aixplorer (Supersonic), L15-4-MHz probe; NR; NR; longitudinal	No	Controls; Age, SBP, **PWV**, LDL-cholesterol	Wall: *AIS:* 83.9 ± 31.2 kPa *Controls*: 61.9 ± 20.6 kPa	Mean, maximal, and SD YM higher in AIS patients than controls (minimal equal) Age, systolic BP, PWV and low LDL-cholesterol positively correlated to YM Optimal YM cutoff values detected AIS mean, maximal, minimal and SD = 55.4, 65.4, 57.5 and 3.2 kPa AUC PWV, mean YM and max YM = 0.55 ± 0.03, 0.59 ± 0.03 and 0.60 ± 0.03 High intra- and inter-group reproducibility (r = 0.755 and r = 0.88)
Garrard et al. 2015	UK	25 symptomatic CVE + scheduled CEA (<7 days)	76 ± 9	16 (64)	Aixplorer (Supersonic), L15-4 MHz probe; NR; NR; longitudinal	No	**Histology** Echogenicity (GSM)	Plaque: *Unstable (n = 9)*††*:* 50.0± 19.6 kPa; *Stable (n = 16):* 79.1±33.8 kPa	Mean YM lower in unstable than stable plaques YM lower for plaques with histologic features related to instability‡‡ YM **not** correlated with GSM

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Table 2 (***Continued***)

Reference	Country	No. of patients	Age (y)*	♂ (%)	Scanner; probe; frequency; push duration; push location; direction	ECG trigger	Comparison†	Mean SWV/YM*,‡	Most important findings
Ramnarine et al. 2014b	UK	81 + clinical carotid US; 54 plaques	76 ± 11	51 (63)	Aixplorer (Supersonic), L15-4 MHz probe; NR; NR; longitudinal	No	**Echogenicity (GSM)** Stenosis percentage Neurologic symptoms	Wall: 42 [37−48] kPa; Plaque: *Symptomatic*‖ *(n = 27)*: 62 ± 6 kPa[1]; *Asymptomatic (n = 20):* 88 ± 9 kPa§§; *GSM*: 1 (n = 7): 20; 2 (n = 14): 35; 3 (n = 21): 42; 4 (n = 12): 63 kPa	YM correlated with GSM in plaques (lower YM in lower GSM) YM lower in symptomatic than asymptomatic plaques YM lower at higher degree of stenosis YM **not** significantly related to age in plaque or vessel wall YM + SR best to predict symptomatic plaques (AUC YM = 0.69, YM + SR = 0.78, GSM = 0.69) Good reproducibility YM with SWE (CV = 22% [vessel wall] and 19% [plaque])

SWV = shear wave velocity; YM = Young's modulus; ROI = region of interest; MRI = magnetic resonance imaging;AHA = American Heart Association; LRNC = lipid-rich necrotic core; IPH = intraplaque hemorrhage; HT = hypertension; NT = normotension; FR = frame rate; PWV = pulse wave velocity; NR = not reported; aSWV = anterior shear wave velocity; BP = blood pressure; pSWV = posterior shear wave velocity; CEA = carotid endarterectomy; CTA = computed tomography angiography; AUC = area under the curve; CCA = common carotid artery; cIMT = carotid intima−media thickness; GSM = gray-scale median; SR = stenosis rate; CV = coefficient of variance; ICC = intraclass correlation coefficient; AIS = acute ischemic stroke; SD = standard deviation; LDL = low-density lipoprotein; CVE = cerebrovascular event; US = ultrasound.

* Reported as ± SD or, if not reported, as interquartile range.

† Boldface indicates the intended reference standard.

‡ Calculated as $YM = 3\rho c^2$, where ρ = tissue density in kg/m^3 and c = SWV in m/s.

§ Value not reported but YMs for soft, mixed, and hard plaques were 11−25, 26−65 and 65 kPa, respectively.

¶ Defined as having one or more vulnerable features: fibrous cap <200 μm, lipid core, intraplaque hemorrhage, inflammatory infiltrate, or intraplaque neovascularization.

‖ Defined as having caused focal neurologic symptoms relating to the ipsilateral brain hemisphere within the past 6-mo period.

\# Although images were not ECG-triggered, SWV was measured in end diastole.

** In case of multiple plaques, the highest-risk plaque, based on the total plaque risk score (based on stenosis percentage, echogenicity, texture grade and surface characteristics) was identified as the patient's representative plaque.

†† Based on the American Heart Association histologic classification (Lovett et al. 2004).

‡‡ Defined as hemorrhage/thrombus, fibrous tissue, large lipid core, foam cells.

§§ SD not reported, so calculated from 95% confidence interval.

Table 3. Characteristics of non-human studies included

Reference	Country	Study type, No. of patients	Scanner; probe type; frequency; push duration; push location; scan direction	ECG trigger	Comparison	Mean SWV/YM	Most important findings
Marlevi et al. 2018	Sweden	*Ex vivo*: 1 aorta (pig) + PVA plaque (24, 10% PVA, 2 × −5 × F/T) + agar surrounding	Verasonics V1, L7-4 probe 4.09-MHz push, FR = 11.7 kHz; 196 μs; 7 locations in anterior wall, posterior wall and plaque; longitudinal	n/a	Cylindrical phantom	*Plaque:* 0.9−8.6 m/s (YM: 2.5−230.8 kPa*), dependent on speed metric + image specification	Frequency bandwidth ≥1 kHz highest ability to differentiate plaque stiffness Phase velocity → YM underestimation in low frequency; accurate values >1 kHz, but high-speed deviation Group velocity → YM underestimation, but highest ability to differentiate plaque stiffness + lowest speed deviation SWVs invariant to push location, but differences in SNR + particle velocity Longitudinal better ability to differentiate plaques than transverse
Shih et al. 2018	Taiwan	*Ex vivo*: 1 abdominal aorta (rabbit) with plaque (lipid-rich diet + $FeCl_3$ injury)	Dual-frequency IVUS, FR = 20 kHz; 200−1000 μs; NR; longitudinal	n/a	n.a.	*Wall*: 3.45 ± 0.45 m/s (YM: 37.13 ± 0.63 kPa*) *Plaque:* 0.38 ± 0.19 m/s (YM: 0.45 ± 0.11 kPa*)	IVUS SWE can distinguish regions of different stiffness SWE acoustic output *in vitro*: max I_{spta} = 412.9 mW/cm^2 (within-safety limits in FDA guideline: <720 [Guidelines for Industry and FDA Staff 2008]) YM differences ≥4.8 kPa can be distinguished
		In vitro: 2 phantoms (gelatin 3% rod, 7% wall + vice versa)		n/a	n.a.	*3% Gelatin:* ca. 0.6 m/s (YM: 1.1 kPa*) *7% Gelatin*: ca. 1.4 m/s (YM: 6.1 kPa*)	
Guo et al. 2018	China	*Ex vivo*: 1 abdominal aorta (pig), no plaque, pressurized	Verasonics, L7-4 probe, Vantage 256, 5 MHz push, FR 8 kHz; 100 μs; anterior wall; longitudinal	n/a	n.a.	*Wall:* Longitudinal 50 kPa; circular 150 kPa	SWE is able to quantify stiffness in many directions, but elasticity values differ with detection angles so geometry correction is needed
		In vitro: 3 homogenous phantoms (15% PVA, 5 × F/T), pressurized		n/a	Mechanical testing	NR† (MT: 100 kPa)	

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Table 3 (***Continued***)

Reference	Country	Study type, No. of patients	Scanner; probe type; frequency; push duration; push location; scan direction	ECG trigger	Comparison	Mean SWV/YM	Most important findings
He et al. 2017	China	*In vivo*: 1 healthy volunteer	Verasonics V1, L10-5 probe, 5 MHz push, FR 14.7 kHz; 170 μs; center anterior wall; transversal	n/a	n.a.	*Wall:* Clockwise 1.9 m/s (YM: 11.3 kPa*) Counterclockwise 1.4 m/s (YM: 6.1 kPa*)	Cross-sectional elasticity assessment with SWE is feasible Phase velocity → good agreement with MT Group velocity → inaccurate elasticity values compared with MT A directional filter can effectively filter out reflected waves
		Ex vivo: 1 abdominal aorta (pig), no plaque		n/a	n.a.	*Wall:* 2.6 m/s (YM: 21.1 kPa*)	
		In vitro: 1 homogenous phantom (10% PVA, 3 × F/T)		**No**	**Mechanical testing**	*Wall:* phase velocity: 90 kPa (MT: 89.1 ± 3.6) kPa), group velocity: 2.8 m/s (YM: 24.5 kPa*)	
Widman et al. 2016	Sweden	*Ex vivo*: 5 thoracic aortas (pig), plaque stiffened with formaldehyde; pressurized	Verasonics, L7-4 probe; 4.09 MHz push, FR up to 10 kHz; 100-700 μs; anterior wall; longitudinal	n/a	n.a.	*Wall*: 258±39 to 522± 105 kPa (*p:*20-120 mmHg) [2‡] *Plaque*: 123±15 to 291± 30 kPa [2]	SWE can measure stiffness in *ex vivo* arteries with different stiffness Linear response in stiffness with respect to BP Frequency bandwidth ≥1.5 kHz needed for consistent YM assessment High PRF more important than higher image quality
Maksuti et al. 2016	Sweden	*In vitro*: 15 phantoms (2 plate, 2 solid cylinder, 11 hollow cylinder; w*all*: 10% PVA, 3 × −5 × F/T), no *plaque,* pressurized	Aixplorer (Supersonic) SL15-4 probe, 5 MHz push, FR 8 kHz; 3 × 150 μs; middle phantom & anterior/posterior wall; longitudinal	**n/a**	**Mechanical testing**	*Wall*: phase velocity: 91.8 ± 9.6; kPa[‡] Group velocity: 20.1 ± 0.0 kPa[‡] (MT: 91.5 ± 1.2) Dependent on pressure + F/T cycles	Phase velocity → accurate stiffness values in vessel phantoms validated with MT (relative error: 8.8 ± 6.0%, absolute error: 5.6 ± 4.1 kPa) Group velocity → inaccurate elasticity values in vessel wall
Widman et al. 2015	Sweden	*In vitro:* 6 phantoms (3 soft, 3 hard plaque; *wall*: 10% PVA, 3 × F/T; *plaques: soft*: 10% PVA, 1 × F/T; *hard*: 10% PVA,	Aixplorer (Supersonic), L15-4 probe, 6 MHz push, FR 8 kHz; 3 × 150 μs; center plaque and anterior wall; longitudinal	**n/a**	**Mechanical testing**	*Wall:* 75.0 ± 3.6 kPa[‡] (MT: 89.1 ± 1.5)[‡] *Plaque: soft* 17.4 ± 0.9 kPa[‡] (MT: 9.9 ± 1.5)[‡]; *hard:* 318.6 ± 51.6 kPa[‡] (MT: 294.9 ± 10.2 [‡]	SWE can assess elasticity is feasible in simulated cardiac cycle Phase velocity → good agreement in plaque and wall with MT (slight over- and underestimation in respective plaques and

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Table 3 (***Continued***)

Reference	Country	Study type, No. of patients	Scanner; probe type; frequency; push duration; push location; scan direction	ECG trigger	Comparison	Mean SWV/YM	Most important findings
		10 × F/T), pressurized					wall) Group velocity → accurate in soft, but inaccurate in hard plaques
Ramnarine et al. 2014a	UK	*In vitro*: 3 phantoms (1 homogenous, 1 hard, 1 soft plaque; *wall*: 10% PVA, 5 × F/T; *plaque*: soft: 5 × F/T; hard: 10% PVA, 7 × F/T), pressurized	Aixplorer (Supersonic) L15-4 probe; NR; NR; longitudinal	n/a	Inter-observer reproducibility	*Wall:* 35−120 kPa depending on pulse/homogeneity *Plaque: soft*: 30−130 kPa; *hard*: 30−260 kPa	Quantitative elasticity assessment with SWE is feasible in vessel wall + different plaque models, even in the presence of pulsatile flow Good reproducibility YM with SWE (mean interframe CV 0.13−0.14 + ICC 0.83−0.84, mean interobserver CV 0.13 + ICC 0.76)
Couade et al. 2010	France	*In vivo*: 1 healthy volunteer (30 y)	Aixplorer (Supersonic), L8 MHz probe, FR 8−10 kHz; 3 × 100 μs; anterior wall; longitudinal	Yes	n.a.	*Wall (diastole/systole):* 80 ± 10/ 130 ± 15 kPa‡	Real-time + quantitative elasticity assessment with SWE is feasible SWE acoustic output *in vivo*: total I_{spta} = 630 mW/cm^2 (within FDA guidelines <720 [Guidelines for Industry and FDA Staff 2008]) + no histologic changes Elastic properties vary during the cardiac cycle Frequency bandwidth >1 kHz best to assess YM in arterial application Shear wave propagation is very dispersive
		In vivo: 10 CCAs (sheep) (48 h after death)		**No**	**Histology**→safety	*Wall (early/late systole):* 117 ± 48/173,519 ± 77 kPa‡	
		In vitro: 8 phantoms (4 plates, 4 tubes, 2% and 4% agar ± background), no plaque, pressurized		n/a	Theoretical model	NR	

ECG = electrocardiogram, SWV = shear wave velocity, YM = Young's modulus, PVA = polyvinyl alcohol, F/T = freeze−thaw cycle, FR = frame rate, SNR = signal-to-noise ratio, IVUS = intravascular ultrasound, NR = not reported; I_{spta} = spatial-peak temporal-average intensity, FDA = U.S. Food and Drug administration MT = mechanical testing, BP = blood pressure, PRF = pulse repetition frequency, CV = coefficient of variance, ICC = intra-class correlation coefficient; CCA = common carotid artery.

* Calculated as YM $= 3\rho c^2$, where ρ = tissue density in kg/m^3 and c = SWV in m/s.

† No value reported because *in vitro* measurements were aimed at defining the default caused by the measurement angle.

‡ Shear modulus (μ) reported, YM calculated as YM $= 3\mu$.

standard, as a reference standard. However, in our opinion, the concerns regarding the methodology of the included studies do not limit their applicability to answering the research question of this review.

Applied ultrasound techniques

The included studies used three different ultrasound machines with different setups. Most studies used an Aixplorer ultrasound system (Supersonic Imagine, Aix-en-Provence, France). Two human studies used a Toshiba Aplio 500 system (Toshiba Medical Systems Co, Ltd, Tokyo, Japan) and one used a General Electric Logiq E9 system (GE Healthcare, Wauwatosa, WI, USA); four non-human studies used a Verasonics system (Verasonics, Kirkland, WA, USA). In all cases a linear array probe was used. In human studies, push frequencies and imaging rates were not reported, except for an imaging frame rate of 8 kHz by Marais et al. (2019). Marlevi et al. (2020) applied a dual-sided push pulse of 400 μs simultaneously triggered in the left- and right-hand sides of the region of interest (ROI). Marais et al. (2019) applied three supersonic pushes of 100 μs at three depths 5 mm apart along the centerline of the ROI, including the anterior and posterior wall. Also, Marais et al. were the only ones to compensate the location of shear wave acquisitions for wall movements during the cardiac cycle using the diameter values measured by echotracking. In the remaining human studies, the clinical mode was used, without a specification of push duration and push location.

In non-human studies, push pulse central frequency, push duration and imaging frame rates ranged from 4.09 MHz (Widman et al. 2016; Marlevi et al. 2018) to 6 MHz (Widman et al. 2015), from 100 μs (Widman et al. 2016; Guo et al. 2018) to 1000 μs (Shih et al. 2018), and from 8 kHz (Couade et al. 2010; Widman et al. 2015; Maksuti et al. 2016; Guo et al. 2018) to 20 kHz (Shih et al. 2018), respectively. The push location varied but was mostlypositioned in the anterior wall.

A representative example of a frequently used method of YM assessment with a commercial ultrasound system (Aixplorer Supersonic Imagine) is the method of Ramnarine et al. (2014b) with circular ROIs, as illustrated in Figure 1. A representative example of a state-of-the-art non-commercially available implementation of group and phase velocity analysis in the longitudinal and cross-sectional imaging direction using raw ultrasound data is the method of Marlevi et al. (2020), illustrated in Figure 2.

SWE IN HUMAN PATIENTS

Study characteristics

The 10 studies on SWE in human carotid arteries (Ramnarine et al. 2014b; Garrard et al. 2015; Maksuti et al. 2016; Zhang et al. 2016; Lou et al. 2017; Alis et al. 2018; Di Leo et al. 2018; Shang et al. 2018; Marais et al. 2019; Marlevi et al. 2020) were performed with varying numbers of patients, that is, 22 (Marlevi et al. 2020) to 199 (Zhang et al. 2016); different diseases affecting the arterial wall, that is, Behçets disease (Alis et al. 2018) and hypertension (Marais et al. 2019); and different stages of atherosclerotic disease, that is, atherosclerotic plaques (Ramnarine et al. 2014b; Zhang et al. 2016; Lou et al. 2017; Marlevi et al. 2020), symptomatic patients with a CEA scheduled (Garrard et al. 2015; Di Leo et al. 2018) or without a CEA scheduled (Maksuti et al. 2016; Shang et al. 2018); and different methods of comparison, that is, pulse wave velocity (PWV) (Maksuti et al. 2016; Marais et al. 2019) and/or healthy controls (Ramnarine et al. 2014b; Maksuti et al. 2016; Alis et al. 2018; Marais et al. 2019) in the arterial wall, and plaque echogenicity (GSM) (Garrard et al. 2015; Zhang et al. 2016; Lou et al. 2017; Shang et al. 2018), neurologic symptoms (Ramnarine et al. 2014b; Lou et al. 2017; Shang et al. 2018), histologic features (Garrard et al. 2015; Di Leo et al. 2018), American Heart Association (AHA) classification of atherosclerotic plaques as assessed with MRI (Marlevi et al. 2020), percentage stenosis (Ramnarine et al. 2014b) and/or other cardiovascular risk factors (Ramnarine et al. 2014b; Maksuti et al. 2016; Zhang et al. 2016; Shang et al. 2018; Marais et al. 2019) in arterial plaques. Because not all patient groups present with atherosclerotic plaques, three studies solely investigated the carotid arterial wall (Maksuti et al. 2016; Alis et al. 2018; Marais et al. 2019). Only one study (Marais et al. 2019) applied echocardiogram (ECG) gating, whereas in the other studies, usually a 10-sec cineloop was recorded and values were averaged over the middle four to five recorded shear wave frames randomly distributed throughout the cardiac cycle. Only Marlevi et al. (2020) focused on SWE in the cross-sectional and longitudinal imaging views whereas others investigated SWE only in the longitudinal imaging view.

Feasibility and value

All studies reported the feasibility of using ultrasound (US) SWE in carotid arteries and found statistically significant differences in elasticity with patient characteristics in both the arterial wall and plaques. In the carotid arterial wall, SWV was higher throughout the entire cardiac cycle higher in patients with hypertension compared with normotensive controls. This difference disappeared when both groups were compared at similar blood pressures (Marais et al. 2019). Behçet's disease (Alis et al. 2018) was, independent of blood pressure, associated with a higher SWV compared with controls. In addition, stiffness values positively correlated with patient characteristics (*i.e.,* age, systolic blood pressure and low-density lipoprotein) in patients with

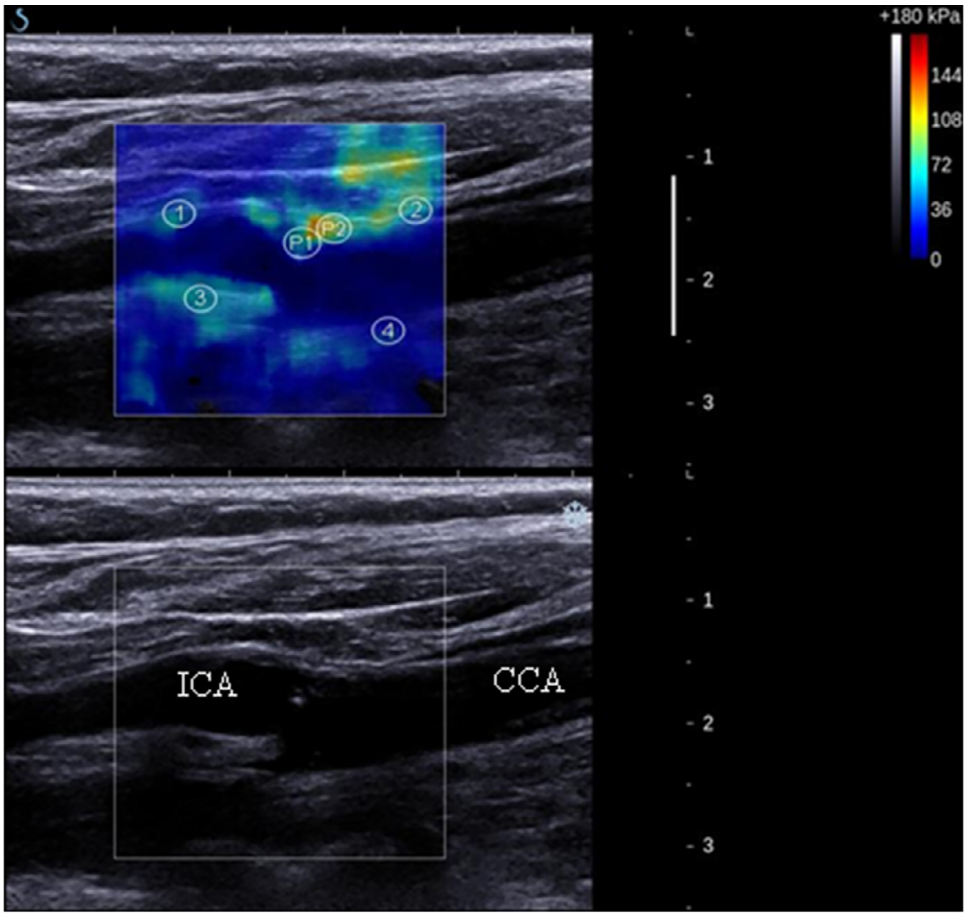

Fig. 1. Example of quantitative stiffness assessment using a commercial ultrasound system (Aixplorer SuperSonic, Aix-en-Provence, France) in a patient with a stenosis of 30%−40% at the origin of the internal carotid artery. Left: B-Mode image with the internal carotid artery (ICA) and common carotid artery (CCA). Right: Elastogram of the ICA and CCA with six 2-mm circular regions of interest in the anterior (2) and posterior (4) CCA, the anterior (1) and posterior (3) ICA, within the plaque (P1 and P2). (Reprinted with permission from Ramnarine et al. [2014b], published under the terms of the Creative Commons Attribution License [http://creativecommons.org/licenses/by/4.0]).

hypertension (Marais et al. 2019) and ischemic stroke (Maksuti et al. 2016).

In carotid artery plaques, stiffness values were significantly lower in plaques with markers of vulnerability, namely, in symptomatic compared with asymptomatic plaques, where symptomatic plaques were defined as having caused focal neurologic symptoms relating to ipsilateral brain hemisphere within the past 6-month period (Ramnarine et al. 2014b; Lou et al. 2017; Shang et al. 2018); in histologically classified vulnerable plaques compared with stable plaques, where vulnerability was defined as having one or more vulnerable features (among others, fibrous cap <200 μm, lipid core and intraplaque hemorrhage) (Garrard et al. 2015; Di Leo et al. 2018); in plaques classified as vulnerable with MRI compared with all other plaque types, where vulnerable plaques were defined as AHA type VI (Marlevi et al. 2020); and, except for the study of Garrard et al. (2015), in hypo-echoic compared with hyper-echoic plaques (Ramnarine et al. 2014b; Zhang et al. 2016; Lou et al. 2017; Shang et al. 2018). In addition, Ramnarine et al. (2014b) found a lower YM in plaques in patients with a higher degree of stenosis; and Zhang et al. (2016) found a lower YM in patients with cardiovascular risk factors (*i.e.,* hyperlipidemia with or without hypertension) compared with patients without these factors.

Quantitative stiffness values

Absolute SWE values vary widely among studies, but within each study, quantitative SWE values significantly differ with respect to patient and plaque characteristics.

Validation and reproducibility

SWE results were in good agreement with results of other imaging techniques and had good to excellent reproducibility. In the carotid arterial wall, SWE velocities were

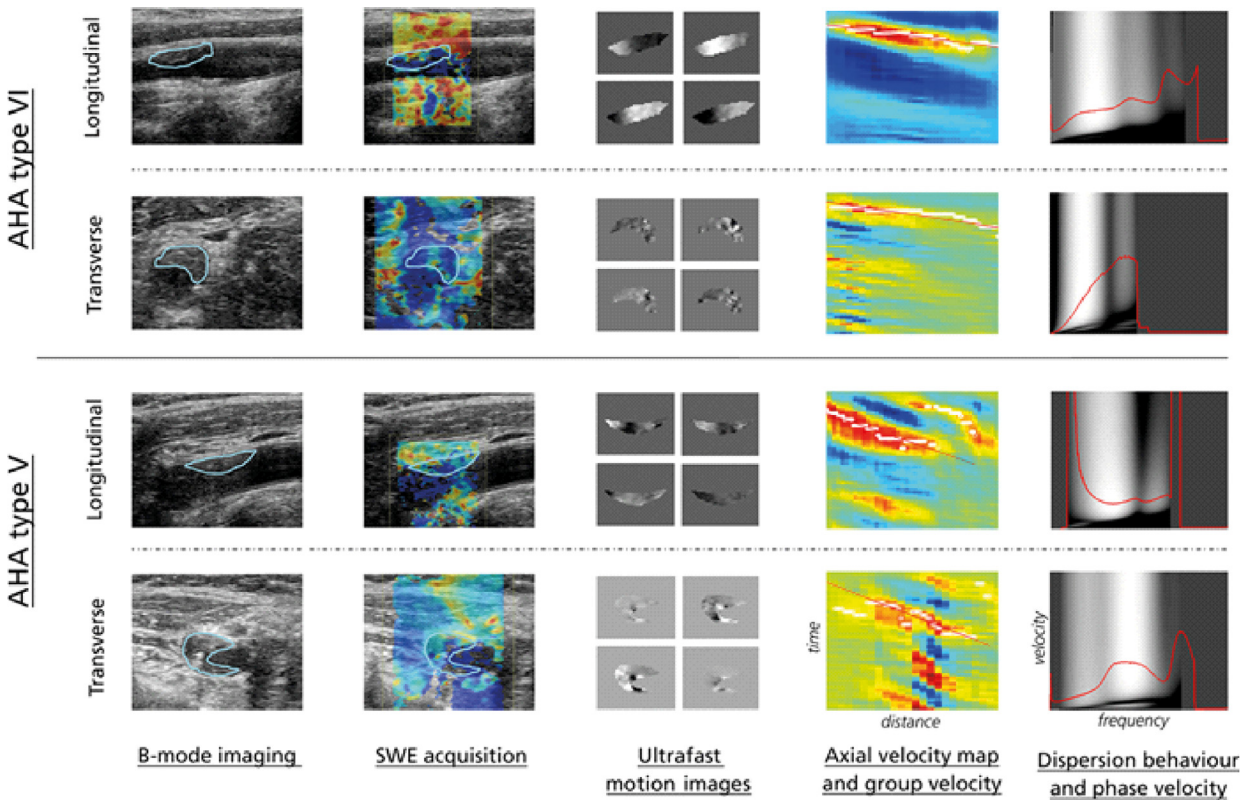

Fig. 2. Example of group and phase velocity analysis in the longitudinal and cross-sectional imaging directions for one American Heart Association (AHA) type VI and one AHA type VI plaque using the raw ultrasound data of a General Electric Logiq E9 system (GE Healthcare, Wauwatosa, WI, USA). From left to right are B-mode images of the carotid artery including the plaque, shear wave elastography (SWE) acquisition, ultrafast motion images obtained from data autocorrelation (from upper left to lower right four snapshot motion images are displayed), axial velocity map (space−time domain) with time-to-peak estimated group velocity (*red slope*) and Fourier-generated dispersion behavior and phase velocity map (velocity−frequency domain). All examples are shown over a frequency range of 0−750 Hz. (Reprinted with permission from Marlevi et al. [2020], published under the terms of the Creative Commons Attribution License [http://creativecommons.org/licenses/by/4.0]).

in good agreement with PWV (*i.e.,* local carotid assessed by US and global carotid-femoral assessed by tonometry with Spearman's correlation coefficients [r] of 0.56 and 0.66, respectively [Marais et al. 2019]) and had a good reproducibility (interframe coefficient of variation [CV] of 22% [Ramnarine et al. 2014b]). However, comparison between the anterior and posterior wall revealed a higher variability in the posterior wall (interframe CV = 20.5% vs. 8.3% [Marais et al. 2019]).

In carotid artery plaques, SWE was in good agreement (81.4%, Cohen's $\kappa = 0.54$) with CTA in detection of histology-based vulnerability with an equal, high, sensitivity of 87.1% but lower specificity (66.7 vs. 100%) (Di Leo et al. 2018). Reproducibility analysis in four studies (Ramnarine et al. 2014b; Maksuti et al. 2016; Zhang et al. 2016; Lou et al. 2017) revealed good to excellent agreement for plaques located anywhere around the arterial wall circumference (*i.e.,* interframe CV of 16%−19%) [Ramnarine et al. 2014b; Lou et al. 2017]).

SWE IN NON-HUMAN PATIENTS

Study characteristics

Nine of the included studies (Couade et al. 2010; Ramnarine et al. 2014a; Maksuti et al. 2016; Widman et al. 2015, 2016; He et al. 2017; Guo et al. 2018; Marlevi et al. 2018; Shih et al. 2018) performed SWE acquisition in non-human patients (*i.e., ex vivo* animal studies and/or *in vitro* phantom studies). Notably, multiple non-human studies applied group and phase velocity analysis in contrast to human studies that, except for one, applied only group velocity. One study (He et al. 2017) included imaging in the cross-sectional imaging view.

Feasibility and tolerability

All studies reported on the feasibility of using SWE to (quantitatively) assess elasticity in a phantom vessel wall and different plaque models, even during a simulated cardiac cycle (Couade et al. 2010; Ramnarine et al.

2014a; Widman et al. 2015, 2016). YM differences of at least 4.8 kPa could be distinguished between different phantom samples (Shih et al. 2018). Stiffness values varied strongly during the cardiac cycle (Couade et al. 2010), whereby both a linear (Widman et al. 2016), and non-linear (Couade et al. 2010) increases in SWV with blood pressure have been reported. Shih et al. (2018) and Couade et al. (2010) evaluated the tolerability of this technique and found that the generated intensities fall within the guidelines from the Food and Drug Administration and there were no histologic changes in the arterial wall after acquisition (Guidelines for Industry and FDA Staff 2008).

Quantitative stiffness values

As in human studies, quantitative SWE values vary widely among non-human studies. Additionally, values between studies are incomparable because the studies used different setups and analysis methods.

Validation and reproducibility

Stiffness values assessed by SWE were more accurate using phase velocity analysis than group velocity analysis. Phase velocity-based YM values were in good agreement with those obtained by mechanical tensile testing (Widman et al. 2015; He et al. 2017; Guo et al. 2018; Marlevi et al. 2018) (relative and absolute errors of 8.8 ± 6.0% and 5.6 ± 4.1 kPa, respectively [Maksuti et al. 2016]). In cases in which group velocity analysis was applied, stiffness values were underestimated (Widman et al. 2015; Maksuti et al. 2016; He et al. 2017; Marlevi et al. 2018), especially in hard plaques (Widman et al. 2015), although the variance of group velocity-based stiffness values was smaller (Marlevi et al. 2018).

Group velocity-based SWE had good reproducibility for YM values (mean inter-frame CV and intra-class correlation coefficient [ICC] of 13−14% and 0.83−0.84 and mean inter-observer CV and ICC of 0.13 and 0.76, respectively [Ramnarine et al. 2014a]).

CROSS-SECTIONAL SWE

He et al. (2017) investigated cross-sectional SWE in a healthy volunteer, an abdominal swine aorta and a PVA phantom, all without plaques. This study found that use of cross-sectional SWE was feasible and in good agreement with mechanical testing in the phantom when phase velocity analysis was applied. Marlevi et al. (2020) additionally found that cross-sectional SWE is able to differentiate vulnerable from stable plaques as defined by the AHA classification and that SWV correlated with intraplaque components associated with plaque vulnerability (*i.e.,* lipid-rich necrotic core content, fibrous cap/necrotic core volume ratio and intraplaque hemorrhage volume). Both differentiability and correlations differed between group and phase velocity analysis settings and between longitudinal and cross-sectional SWE.

ADDITIONS FROM ABSTRACTS/PROCEEDINGS

Abstracts and proceedings mainly endorse the results stated above but additionally reported that:

- Tracking of cross-sectional shear wave propagation is less accurate because the shear wave propagation does not remain aligned with the ultrasound image lines.
- The shear wave exhibited more dispersive behavior in the cross-sectional view than in the longitudinal view, possibly because of the curved cross-sectional geometry.
- Imaging is limited in highly calcified plaques because of acoustic shadowing.
- SWV and mean and median longitudinal-to-transverse SWV ratio are higher in the case of longer statin therapy (≥5 vs. <5 y).
- SWV is similar in plaques with and without intraplaque neovascularization.

DISCUSSION

To assess the feasibility and diagnostic value of using SWE in (mimicked) atherosclerotic arteries, a heterogeneous collection of studies including human and non-human patients was included in this systematic review. All studies reported on the feasibility of using this technique to assess elasticity in the carotid arterial wall and plaques separately. Absolute SWE values varied widely among studies, but within each study, statistically significant differences in elasticity with patient characteristics were found. US SWE could assess plaque vulnerability based on histology, symptoms, echogenicity and AHA classification of plaque type. Quantitative elasticity measurements were in good agreement with CTA and PWV in human studies and, in cases in which phase velocity analysis was applied, with mechanical testing in non-human studies. Good to excellent reproducibility was also reported. A preliminary study on cross-sectional SWE reported its feasibility.

To our knowledge, only one systematic review was previously published on vascular SWE using US that reported results similar to the results in this review. This review by Mahmood et al. in 2016 evaluated the applicability of US elastography to assessment of carotid artery plaque vulnerability. Mainly studies using strain were included; only three articles used SWE in carotid arteries. They concluded that elastography was feasible and vulnerable plaques mostly had higher strain values. This corresponds to the lower quantitative stiffness values in vulnerable plaques found in this review.

SWE in human studies

Feasibility and value. Higher stiffness values in the carotid arterial wall with hypertension are expected because Couade et al. (2010) reported that SWV increases with higher pressures. However, the higher stiffness values found in the carotid arterial wall in cases of Behçet's disease and in the presence of cardiovascular risk factors other than hypertension, compared with healthy controls, may point to the potential of SWE in assessment of vascular health. However, multiple factors influence arterial elasticity that have to be considered when evaluating individuals:

- *Personal factors:* Age, genetics, blood pressure, heart rate and different diseases (*e.g.,* diabetes mellitus type 2, cardiovascular and renal disease, pre-eclampsia [Benetos et al. 2002; Patel et al. 2016] and inflammatory diseases such as rheumatoid arthritis [Mozos et al. 2017]).
- *Lifestyle factors:* Exercise, diet (Sacre Julian et al. 2014) and smoking (Patel et al. 2016).
- *Extrinsic factors*: Medical treatment (*e.g.*, lipid-lowering or antihypertensive medication) [Janić et al. 2014], acquisition characteristics (*i.e.,* spatial and temporal filtering, neck position, pressure applied with the US probe) [Bamber et al. 2013] and timing during the cardiac cycle (*e.g.,* arterial diameter changes resulting from pressure differences within the cardiac cycle) [Couade et al. 2010].

Changes in arterial stiffness are caused by alterations in structural and functional components of the artery. These alterations often also cause a change in IMT, which in itself is one of the key biomarkers of cardiovascular disease (Yuan et al. 2013).

The lower elasticity values found in hypo-echoic plaques compared with hyper-echoic plaques might suggest that SWE can identify plaque vulnerability because several studies found a relation between echogenicity and plaque vulnerability: (i) histopathology studies reported more vulnerability features (*i.e.,* more lipid, less calcification and increased macrophage density) in hypo-echoic than hyper-echoic plaques (Gronholdt et al. 2002), and (ii) US studies reported a higher prevalence of future ipsilateral stroke in hypo-echoic than hyper-echoic plaques over all stenosis severities (stenoses of 0−99% and >50% are associated with relative risks of 2.31 and 1.62, respectively [Gupta et al. 2015], respectively, and an odds ratio of 3.99 [Brinjikji et al. 2015]).

SWE, however, may be superior to echogenicity in identifying vulnerable plaques. Echogenicity provides an indication of plaque composition but does not absolutely assess it, and a poor reproducibility has been described (Kanber et al. 2013). Care should thus be taken to correlate echogenicity with plaque vulnerability. The fact that Garrard et al. (2015) used echogenicity to define vulnerability may therefore be the reason that only they did not find a correlation between elasticity and GSM. The small number of patients (n = 25) and the significantly higher proportion of severe stenosis in patients with unstable plaques (89% vs. 44%) could have influenced the results. Nevertheless, because YM values were lower in histologic vulnerable plaques, SWE may be superior to echogenicity in assessing plaque vulnerability. This technique's potential in vulnerability assessment is confirmed by the high sensitivity of SWE in detection of histologic vulnerable plaques reported by Di Leo et al. (2018).

The validity of SWE is also emphasized by conference abstracts that reported lower mean and median longitudinal-to-transverse SWV ratios and, therefore, higher stiffness of plaques to be associated with prolonged statin therapy. This is expected because stroke incidence decreases with statin therapy.

Eventually, the correlation between elasticity and symptomatology is the most important measure because a CEA would be beneficial in patients with (previous or future) neurologic symptoms. Therefore, the reported relationship between symptomatology and lower stiffness values assessed by SWE, further emphasizes this technique's potential in improving personalized stroke risk stratification.

Quantitative stiffness values

Although differences in stiffness values with plaque vulnerability within each study were statistically significant, the high variability between studies needs to be reduced in the future to establish cutoff values to distinguish vulnerable from non-vulnerable plaques. The heterogeneity between studies can be caused by multiple study characteristics. First, by the use of different US machines as acquisition and post-processing properties differ with the machine. Alis et al. (2018) reported considerably lower stiffness values in the arterial wall than the other studies. They used a Toshiba Aplio 500 machine that does not have a specific carotid artery mode. Therefore, push location, assumed propagation trajectory, push moment during cardiac cycle and amount of spatial and temporal smoothing were unclear. The remaining human studies used an Aixplorer (Supersonic Imagine) machine. This system induces multiple pushes along the beam axis, resulting in an amplified shear wave strength and a planar shear wave propagation front (Bamber et al. 2013). It is optimized for bulk tissues (Couade et al. 2010) and most valid in the liver. However, vessel stiffness measurements may be inaccurate with this machine because stiffness is more difficult

to assess in vessels because they are small, subject to pulsatile motion, anisotropic and of heterogenous composition (Ramnarine et al. 2014a).

Second, the method of YM calculation may be responsible. The YM is calculated as YM = $3\rho c^2$, where ρ = tissue density (in kg/m^3), and c is the SWV (in m/s) (Bamber et al. 2013). However, this formula is accurate only for incompressible, infinitely large, isotropic and locally homogeneous material—all characteristics that do not apply to real arteries. In addition, calculations are performed with an average soft tissue density, whereas the density is known to vary. Some ultrasound machines enable the acquisition of raw data that allows use of different post-processing techniques to correct for some of these errors, while most applied scanners display only the calculated values that cannot be corrected retrospectively.

Third, different areas and locations of analysis were used. The area of analysis in the clinical scanners ranged from multiple ROIs of 1−2 mm to a manually drawn area around the vascular wall or entire plaque. This, in a different manner, accounts for regional stiffness variances.

Fourth, it is important to consider temporal differences in quantitative values, because SWE values have been reported to vary between the diastolic (80 ± 10 kPa) and systolic (130 ± 15 kPa) phases (Couade et al. 2010). Only one human study applied ECG gating to correct for these differences; all other studies averaged the SWE values over different frames during the cardiac cycle, complicating their comparison. SWE with a high temporal resolution and ECG gating are needed to improve the comparability between studies.

The high variability in quantitative values between studies impedes the identification of cutoff values for physiologic or pathologic stiffness in the arterial wall and plaques. Further research with standardized methodology and improved data analysis might overcome this problem.

Validation and reproducibility

SWE is thought to be more reliable than traditional ultrasound and PWV in assessing elasticity, which is in accordance with the good to excellent reproducibility of SWE described in this review. SWE is less operator and experience dependent than traditional ultrasound examination (Lou et al. 2017). Furthermore, SWE would be more reliable than the frequently used global PWV (Couade et al. 2010). SWE assesses elasticity directly, locally and at a user-defined moment during the cardiac cycle, whereas global PWV assesses elasticity averaged over a long arterial distance (typically the aorta), which is in itself already difficult to assess.

Interesting findings by Marais et al. (2019) were the higher stiffness values and, even more striking, the higher variance in the posterior than in the anterior arterial wall. These are important findings because plaques can be located over the entire wall circumference. The higher variance in the posterior compared with the anterior wall can be caused by a lower signal quality because of the larger distance from the transducer. The larger distance induces more attenuation and presumably more reflections and reverberations originating from the overlying soft tissue (Couade et al. 2010). Another possible cause is the anatomic location of both walls: the anterior wall is located directly below the jugular vein, but well separated from the other surrounding tissues, allowing it to move freely; the posterior wall is directly attached to the muscle layer beneath it, possibly affecting movement and elasticity to a greater extent. Also, neck position, and therefore stretch on the carotid artery, might be a confounding factor (Bamber et al. 2013). Improved instrumentation and acquisition parameters (*e.g.,* push depth, resolution and increasing the energy efficiency of the transducer elements) may overcome these limitations.

Although it has been reported that SWE provides a resolution of approximately 0.30 mm^2 (Marlevi et al. 2020), to date, *in vivo* SWE studies have not performed a regional analysis of plaques but report instead average shear wave estimates for ROIs encompassing the whole plaque (1−2 cm^2). Although average values seemed to correlate with plaque components assessed by MRI (Marlevi et al. 2020), plaque components might be better distinguished with regional analyses, especially in plaques with mixed compositions.

Studies in non-human patients

Feasibility and tolerability. Non-human studies evaluated the tolerability of SWE, but more research is needed to make a definite assessment. The main concern in SWE application is the possibility of plaque rupture caused by the induced push, although Doherty et al. (2013) found that stress induced by the ARFI push pulse was three orders of magnitude lower than stress induced by the blood pressure. Additional studies in human plaques are required to definitely assess the influence of SWE on plaque rupture.

Validation and reproducibility. In clinical practice, elasticity is assessed using group velocity analysis, but absolute values assessed using phase velocity analysis might be more accurate, especially for stiffer plaques, as non-human studies have reported more accurate stiffness values in the latter case. Dispersion, which is not taken into account in group velocity analysis, probably causes this difference. Dispersion is a result of tissue viscosity, which has also been reported in PVA when measured with atomic force microscopy (Yang et al. 2009), and of the confined geometry of the vessel wall that strongly affects shear wave propagation. The wavelengths of the shear waves

generated are in the range of millimeters, similar to phantom or vessel thickness. Internal reflections at the medium's boundaries do, therefore, strongly affect their propagation. Exact geometry becomes less important at higher frequencies (>1000 Hz) because the shear wave wavelength becomes smaller compared with the wall thickness (Couade et al. 2010). However, with higher frequencies, there is also more attenuation. A trade-off between wavelength and attenuation must therefore be made.

Imaging settings. Most non-human studies were performed to evaluate new mathematical models or data processing techniques, giving rise to recommendations regarding SWE acquisitions. To accurately assess elasticity values, non-human studies emphasize that:

- High-frequency bandwidths, that is, including frequencies greater than 1 kHz (Couade et al. 2010; Marlevi et al. 2018) or 1.5 kHz (Widman et al. 2016), need to be excited because of the dispersion phenomenon resulting from the confined geometry that occurs at lower frequencies.
- A high pulse repetition frequency (PRF) is needed to accurately assess SWV, especially in tissues subject to high pressure or with higher stiffness. Because the shear wave travels faster in these tissues, a higher PRF is needed to acquire the same number of images of the shear wave and, therefore, to assess the SWV with the same accuracy. A high PRF is even more important than image quality (Widman et al. 2016).
- The optimal push location needs to be chosen. Although the SWV estimation does not change with push location, different push locations are associated with changes in signal-to-noise ratio and maximum particle velocity (Marlevi et al. 2018).
- The geometry of the vessel is dependent on the acquisition angle (*e.g.,* the angle with respect to the longitudinal direction of the vessel). In some cases, this view-dependent altered geometry can cause overestimation of YM, so a correction for an induced difference in geometry needs to be applied (Guo et al. 2018).

Non-human studies also underline the influence of pressure differences on stiffness values and, therefore, the necessity to assess stiffness at a precise time within the cardiac cycle. Arterial wall stiffness increases when arterial pressure increases. Therefore, stiffness values will vary with blood pressure and pressure differences throughout the cardiac cycle. The fact that this response between stiffness and pressure is reported to be both linear and non-linear by different studies could be explained by the elastin−collagen model. In case of low stress (blood pressure <100 mm Hg) elastin fibers will stiffen the artery with increasing pressure. In case of higher stress (blood pressure >100 mm Hg), when elastin fibers are already fully stressed, collagen fibers are recruited for the stiffening of the arteries (Callaghan et al. 1986). Because the two types of fibers have different mechanical properties, their elasticity does not respond identically to changes in stress.

Cross-sectional SWE

Combining longitudinal and cross-sectional SWE might improve the accuracy of SWE. Because of the anisotropy of vessel walls (Shcherbakova et al. 2015), longitudinal measurements cannot completely evaluate elasticity along the arterial circumference. Additionally, not all plaques can be imaged optimally in the longitudinal direction because they may also be located on the side walls of the artery. Eccentrically located plaques have even been associated with a significantly increased incidence of ipsilateral cerebrovascular events in large clinical trials (Ohara et al. 2008).

Cross-sectional SWE can overcome this limitation and has successfully been applied in the carotid arterial wall (Hansen et al. 2015; He et al. 2017; Marlevi et al. 2020) but remains challenging. Difficulties in propagation tracking caused by fast attenuation and the failure of the particle motion resulting from shear wave propagation to remain aligned with the ultrasound image lines need to be overcome before it can be clinically implemented.

Limitations

This systematic review has several limitations. First, the heterogeneity of the included studies in terms of study type (*i.e., in vivo, ex vivo* or *in vitro*), disease characteristics, number of patients, applied ultrasound machines and settings, number of measurements, push location, methods of comparison, and type of reported data. This heterogeneity markedly hampers comparison between different studies. Second, only a small number of patients and a relatively small number of human studies have been published. Moreover, only one study was performed prospectively, and no follow-up studies were performed. Additionally, plaques are usually evaluated after a cardiovascular event is detected. Therefore, stiffness before the CEA is unknown, although this would probably be a more important measure for stroke risk stratification.

Although studies in non-human patients mimic the situation in human arteries, there are multiple concerns over the applicability of these studies in humans *in vivo*. In contrast to PVA phantoms, real vessels are more heterogeneous with multiple layers with different elasticity (Shcherbakova et al. 2015), are anisotropic (Chai et al. 2013; Shcherbakova et al. 2015), often contain

calcifications causing shadowing, are viscoelastic and have been considered compressible and incompressible in conflicting studies (Yosibash et al. 2014). Furthermore, most studies were performed in water, while *in vivo* carotid arteries are surrounded by other attenuating tissues such as muscles, fat, veins and nerves.

Further research, ideally large, longitudinal, prospective clinical studies in patients before and after symptom occurrence in a longitudinal and circumferential direction, including histologic evaluation, is needed to better evaluate this technique's prognostic accuracy, reproducibility and quantitative value.

CONCLUSIONS

This systematic review focused on the feasibility of US SWE in vascular applications and its ability to contribute to plaque characterization. Ischemic strokes are widespread, highly immobilizing conditions, so risk stratification is very important. However, current clinical practice remains suboptimal. To improve this situation, this systematic review aimed to investigate the feasibility and diagnostic value of vascular US SWE in (mimicked) arteries affected by different stages of atherosclerotic disease or diseases related to atherosclerosis, to eventually develop a more personalized stroke risk stratification. All studies reported the feasibility of using SWE (quantitatively) to assess stiffness of the arterial wall and plaques and to assess plaque vulnerability based on echogenicity, symptomatology and histology with good to excellent reproducibility. These findings confirm its potential to improve stroke risk stratification. However, further technical and clinical research is needed to optimize and standardize its performance and to explore and confirm its true diagnostic value.

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Conflict of interest disclosure—The authors declare that they have no conflict of interest.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ultrasmedbio.2020.05.013.

REFERENCES

Alis D, Durmaz ESM, Civcik C, Tutuncu M, Saip S, Kocer N, Islak C, Kizilkilic O. Assessment of the common carotid artery wall stiffness by shear wave elastography in Behcet's disease. Med Ultrason 2018;20:446–452.

Bamber J, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, Cantisani V, Correas JM, D'Onofrio M, Drakonaki EE, Fink M, Friedrich-Rust M, Gilja OH, Havre RF, Jenssen C, Klauser AS, Ohlinger R, Saftoiu A, Schaefer F, Sporea I, Piscaglia F. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography: Part 1. Basic principles and technology. Ultraschall Med 2013;34:169–184.

Benetos A, Waeber B, Izzo J, Mitchell G, Resnick L, Asmar R, Safar M. Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: Clinical applications. Am J Hypertens 2002;15:1101–1108.

Bernal M, Nenadic I, Urban MW, Greenleaf JF. Material property estimation for tubes and arteries using ultrasound radiation force and analysis of propagating modes. J Acoust Soc Am 2011;129:1344–1354.

Brinjikji W, Rabinstein AA, Lanzino G, Murad MH, Williamson EE, DeMarco JK, Huston J, III. Ultrasound characteristics of symptomatic carotid plaques: A systematic review and meta-analysis. Cerebrovasc Dis 2015;40:165–174.

Callaghan FJ, Geddes LA, Babbs CF, Bourland JD. Relationship between pulse-wave velocity and arterial elasticity. Med Biol Eng Comput 1986;24:248–254.

Chai CK, Akyildiz AC, Speelman L, Gijsen FJH, Oomens CWJ, van Sambeek MRHM, van der Lugt A, Baaijens FPT. Local axial compressive mechanical properties of human carotid atherosclerotic plaques—Characterisation by indentation test and inverse finite element analysis. J Biomech 2013;46:1759–1766.

Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN, Cote R, Hess D, Saver J, Spence JD, Stern B, Wilterdink J, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Carotid endarterectomy—An evidence-based review: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2005;65:794–801.

Coolen BF, Poot DH, Liem MI, Smits LP, Gao S, Kotek G, Klein S, Nederveen AJ. Three-dimensional quantitative T1 and T2 mapping of the carotid artery: Sequence design and in vivo feasibility. Magn Reson Med 2016;75:1008–1017.

Couade M, Pernot M, Prada C, Messas E, Emmerich J, Bruneval P, Criton A, Fink M, Tanter M. Quantitative assessment of arterial wall biomechanical properties using shear wave imaging. Ultrasound Med Biol 2010;36:1662–1676.

Coutinho JM, Derkatch S, Potvin ARJ, Tomlinson G, Kiehl TR, Silver FL, Mandell DM. Nonstenotic carotid plaque on CT angiography in patients with cryptogenic stroke. Neurology 2016;87:665–672.

Di Leo N, Venturini L, de Soccio V, Forte V, Lucchetti P, Cerone G, Alagna G, Caratozzolo M, Messineo D, Di Gioia C, Di Marzo L, Fresilli D, De Vito C, Pugliese G, Cantisani V, D'Ambrosio F. Multiparametric ultrasound evaluation with CEUS and shear wave elastography for carotid plaque risk stratification. J Ultrasound 2018;21:293–300.

Doherty JR, Dumont DM, Trahey GE, Palmeri ML. Acoustic radiation force impulse imaging of vulnerable plaques: A finite element method parametric analysis. J Biomech 2013;46:83–90.

Fisher M, Paganini-Hill A, Martin A, Cosgrove M, Toole JF, Barnett HJ, Norris J. Carotid plaque pathology: Thrombosis, ulceration, and stroke pathogenesis. Stroke 2005;36:253–257.

Flaherty ML, Kissela B, Khoury JC, Alwell K, Moomaw CJ, Woo D, Khatri P, Ferioli S, Adeoye O, Broderick JP, Kleindorfer D. Carotid artery stenosis as a cause of stroke. Neuroepidemiology 2013;40:36–41.

Freilinger TM, Schindler A, Schmidt C, Grimm J, Cyran C, Schwarz F, Bamberg F, Linn J, Reiser M, Yuan C, Nikolaou K, Dichgans M, Saam T. Prevalence of nonstenosing, complicated atherosclerotic plaques in cryptogenic stroke. JACC Cardiovasc Imaging 2012;5:397–405.

Garrard JW, Ummur P, Nduwayo S, Kanber B, Hartshorne TC, West KP, Moore D, Robinson TG, Ramnarine KV. Shear wave elastography may be superior to greyscale median for the identification of carotid plaque vulnerability: A comparison with histology. Ultraschall Med 2015;36:386–390.

Global Burden of Disease Study (GBDS) Collaborators. Global, regional, and national burden of stroke, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:439–458.

Graff KF. Wave motion in elastic solids. New York: Dover; 1991.

Gronholdt ML, Nordestgaard BG, Bentzon J, Wiebe BM, Zhou J, Falk E, Sillesen H. Macrophages are associated with lipid-rich carotid artery plaques, echolucency on B-mode imaging, and elevated plasma lipid levels. J Vasc Surg 2002;35:137–145.

Guidance for Industry and FDA staff [electronic resource]. Interactive review for medical device submissions, 510(k)s, original PMAs, PMA supplements, original BLAs, and BLA supplements. Rockville, MD: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health/Center for Biologics Evaluation and Research; 2008.

Guo Y, Wang Y, Chang EJ, Lee WN. Multidirectional estimation of arterial stiffness using vascular guided wave imaging with geometry correction. Ultrasound Med Biol 2018;44:884–896.

Gupta A, Kesavabhotla K, Baradaran H, Kamel H, Pandya A, Giambrone AE, Wright D, Pain KJ, Mtui EE, Suri JS, Sanelli PC, Mushlin AI. Plaque echolucency and stroke risk in asymptomatic carotid stenosis: A systematic review and meta-analysis. Stroke 2015;46:91–97.

Hansen HHG, Pernot M, Chatelin S, Tanter M, de Korte CL. Shear wave elastography for lipid content detection in transverse arterial cross-sections. Taipei: IEEE International Ultrasonics Symposium (IUS); 2015. p. 1–4 2015.

Hansen HH, de Borst GJ, Bots ML, Moll FL, Pasterkamp G, de Korte CL. Validation of noninvasive in vivo compound ultrasound strain imaging using histologic plaque vulnerability features. Stroke 2016;47:2770–2775.

He Q, Li GY, Lee FF, Zhang Q, Cao Y, Luo J. Novel method for vessel cross-sectional shear wave imaging. Ultrasound Med Biol 2017;43:1520–1532.

Horie N, Morikawa M, Ishizaka S, Takeshita T, So G, Hayashi K, Suyama K, Nagata I. Assessment of carotid plaque stability based on the dynamic enhancement pattern in plaque components with multidetector CT angiography. Stroke 2012;43:393–398.

Janić M, Lunder M, Sabovič M. Arterial stiffness and cardiovascular therapy. Biomed Res Int 2014;2014 621437.

Kanber B, Hartshorne TC, Horsfield MA, Naylor AR, Robinson TG, Ramnarine KV. Dynamic variations in the ultrasound greyscale median of carotid artery plaques. Cardiovasc Ultrasound 2013;11:21.

Li Z, Du L, Wang F, Luo X. Assessment of the arterial stiffness in patients with acute ischemic stroke using longitudinal elasticity modulus measurements obtained with shear wave elastography. Med Ultrason 2016;18:182–189.

Lou Z, Yang J, Tang L, Jin Y, Zhang J, Liu C, Li Q. Shear wave elastography imaging for the features of symptomatic carotid plaques: A feasibility study. J Ultrasound Med 2017;36:1213–1223.

Lovett JK, Gallagher PJ, Hands LJ, Walton J, Rothwell PM. Histological correlates of carotid plaque surface morphology on lumen contrast imaging. Circulation 2004;110:2190–2197.

Mahmood B, Ewertsen C, Carlsen J, Nielsen MB. Ultrasound vascular elastography as a tool for assessing atherosclerotic plaques - A systematic literature review. Ultrasound Int Open 2016;2:E106–E112.

Maksuti E, Widman E, Larsson D, Urban MW, Larsson M, Bjällmark A. Arterial stiffness estimation by shear wave elastography: Validation in phantoms with mechanical testing. Ultrasound Med Biol 2016;42:308–321.

Marais L, Pernot M, Khettab H, Tanter M, Messas E, Zidi M, Laurent S, Boutouyrie P. Arterial stiffness assessment by shear wave elastography and ultrafast pulse wave imaging: Comparison with reference techniques in normotensives and hypertensives. Ultrasound Med Biol 2019;45:758–772.

Marlevi D, Maksuti E, Urban MW, Winter R, Larsson M. Plaque characterization using shear wave elastography—Evaluation of differentiability and accuracy using a combined ex vivo and in vitro setup. Phys Med Biol 2018;63 235008.

Marlevi D, Mulvagh SL, Huang R, Kevin DeMarco J, Ota H, Huston J, III, Winter R, Macedo TA, Abdelmoneim SS, Larsson M, Pellikka PA, Urban MW. Combined spatiotemporal and frequency-dependent shear wave elastography enables detection of vulnerable carotid plaques as validated by MRI. Sci Rep 2020;10:403.

Mozos I, Malainer C, Horbańczuk J, Gug C, Stoian D, Luca CT, Atanasov AG. Inflammatory markers for arterial stiffness in cardiovascular diseases. Front Immunol 2017;8:1058.

Ohara T, Toyoda K, Otsubo R, Nagatsuka K, Kubota Y, Yasaka M, Naritomi H, Minematsu K. Eccentric stenosis of the carotid artery associated with ipsilateral cerebrovascular events. Am J Neuroradiol 2008;29:1200–1203.

Patel AK, Suri HS, Singh J, Kumar D, Shafique S, Nicolaides A, Jain SK, Saba L, Gupta A, Laird JR, Giannopoulos A, Suri JS. A review on atherosclerotic biology, wall stiffness, physics of elasticity, and its ultrasound-based measurement. Curr Atheroscler Rep 2016;18:83.

Ramnarine KV, Garrard JW, Dexter K, Nduwayo S, Panerai RB, Robinson TG. Shear wave elastography assessment of carotid plaque stiffness: In vitro reproducibility study. Ultrasound Med Biol 2014;40:200–209.

Ramnarine KV, Garrard JW, Kanber B, Nduwayo S, Hartshorne TC, Robinson TG. Shear wave elastography imaging of carotid plaques: Feasible, reproducible and of clinical potential. Cardiovasc Ultrasound 2014;12:49.

Sacre Julian W, Jennings Garry LR, Kingwell Bronwyn A. Exercise and dietary influences on arterial stiffness in cardiometabolic disease. Hypertension 2014;63:888–893.

Sarvazyan AP, Rudenko OV, Swanson SD, Fowlkes JB, Emelianov SY. Shear wave elasticity imaging: A new ultrasonic technology of medical diagnostics. Ultrasound Med Biol 1998;24:1419–1435.

Shang J, Wang W, Feng J, Luo GG, Dang Y, Sun J, Yang YQ, Ruan LT. Carotid plaque stiffness measured with supersonic shear imaging and its correlation with serum homocysteine level in ischemic stroke patients. Korean J Radiol 2018;19:15–22.

Shcherbakova DA, Papadacci C, Swillens A, Caenen A, De Bock S, Saey V, Chiers K, Tanter M, Greenwald SE, Pernot M, Segers P. Supersonic shear wave imaging to assess arterial nonlinear behavior and anisotropy: Proof of principle via ex vivo testing of the horse aorta. Adv Mech Eng 2015;6 272586.

Shih C, Qian X, Ma T, Han Z, Huang C, Zhou Q, Shung KK. Quantitative assessment of thin-layer tissue viscoelastic properties using ultrasonic micro-elastography with Lamb wave model. IEEE Trans Med Imaging 2018;37:1887–1898.

Spagnoli LG, Mauriello A, Sangiorgi G, Fratoni S, Bonanno E, Schwartz RS, Piepgras DG, Pistolese R, Ippoliti A, Holmes DR, Jr. Extracranial thrombotically active carotid plaque as a risk factor for ischemic stroke. JAMA 2004;292:1845–1852.

Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–536.

Widman E, Maksuti E, Larsson D, Urban MW, Bjallmark A, Larsson M. Shear wave elastography plaque characterization with mechanical testing validation: A phantom study. Phys Med Biol 2015;60:3151–3174.

Widman E, Maksuti E, Amador C, Urban MW, Caidahl K, Larsson M. Shear wave elastography quantifies stiffness in ex vivo porcine artery with stiffened arterial region. Ultrasound Med Biol 2016;42:2423–2435.

Yang N, Kar K, Wong H, de Bruyn JR, Hutter JL. Frequency-dependent viscoelasticity measurement by atomic force microscopy. Meas Sci Technol 2009;20:25703–25709.

Yosibash Z, Manor I, Gilad I, Willentz U. Experimental evidence of the compressibility of arteries. J Mech Behav Biomed Mater 2014;39:339–354.

Yuan LJ, Xue D, Duan YY, Cao TS, Yang HG, Zhou N. Carotid arterial intima–media thickness and arterial stiffness in pre-eclampsia: Analysis with a radiofrequency ultrasound technique. Ultrasound Obstet Gynecol 2013;42:644–652.

Zhang L, Yong Q, Pu TN, Lin J. Quantitative assessment of carotid atherosclerotic plaque: Initial clinical results using ShearWave elastography. Int J Clin Exp Med 2016;9:9347–9355.